REMARKS

I. Claim Status

Claims 1-40 were originally pending, claims 1-15 and 25-40 were withdrawn from examination prior to the Office Action of July 13, 2010, and claims 17-19 and 21-22 were canceled by Amendment on January 12, 2011. With the above Amendment, Applicants cancel independent claim 16, and dependent claims 20, 23 and 24, the only claims under examination prior to this Amendment. While the language of claim 41 differs from the language of canceled claim 16 in that it more particularly points out the features on the invention, new claims 41-43 effectively replace claims 16, 20, and 23, respectively. Claims 42 and 43 differ slightly from canceled claims 20 and 23 in that the language of the claims is consistent with that of claim 41. The Amendment is supported by the as-filed claims, as well as by claim 16, as previously amended. Because claim 41 incorporates the subject matter of claim 24, claim 24 is canceled. Thus, no new matter is introduced by this Amendment.

II. Summary of Interview

Applicants appreciate the willingness of the Examiner to meet with Applicants' representatives on August 30, 2011. The Examiner has provided a detailed summary of the interview. While Applicants do not necessarily agree with each particular, the Examiner's Summary of Record of Interview dated September 8, 2011, describes the substance of the discussion at the interview. This response has been prepared in light of the interview. Applicants respectfully request review of this application based on this response to the actualrejections in the Office Action.

III. **Rejection under 35 U.S.C. § 112, second paragraph**

Claims 16, 20, 23, and 24 were rejected by the Office under 35 U.S.C. § 112, second paragraph, as being indefinite. Office Action at 3. According to the Office, the term "substantially" in claim 16 is a relative term that renders the claim indefinite. *Id.* Specifically, the Office alleges that the specification does not provide a standard for ascertaining the requisite degree [to which the formation of the stem loop structure is disrupted]. *Id.*

While Applicants respectfully disagree with the Office's conclusion regarding claim 16's recitation of the term "substantially," Applicants point out that new claim 41, which replaces claim 16 no longer recites the term "substantially," and thus the Amendment renders the rejection moot. New claim 41 emphasizes the structure of the claimed oligonucleotide sequence. Because the term "substantially" had been used in the claim to describe a functional feature of the invention, *i.e.*, the disruption of the stem loop, its removal from the claims is merely tangential, and in no way alters Applicants' characterization of the disruption of the claimed stem loop when the complex binds a target sequence.

IV. **Rejection under 35 U.S.C. § 112, first paragraph**

Claims 16, 20, 23, and 24 were rejected by the Office under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Office Action at 3. As new claims 41-43 replace claims 16, 20, and 23, and claim 24 is canceled, the following remarks effectively apply to the new claims.

According to the Office, Applicants have claimed a genus of nucleic acid complexes, that, "at the very least . . . comprise two molecules an - oligonucleotide

comprising a hairpin-forming sequence capable of forming a stem-loop, and a 'fluorophore-labeled reporter sequence'." *Id.* at 5. The Office then points out that the specification discloses, "[a]s used herein, an oligonucleotide can be a polynucleotide and comprise at least 10, 20, 30, 40, 50, or more nucleotide residues." *Id.* at 5, (citing the specification at 10). Focusing on the phrase "at least 10, 20, 30, 40, 50, or more nucleotide residues," the Office concludes that "[a] review of the disclosure fails to find where applicant has described any oligonucleotide, useful or not, that is 10, 30, 40, 50 or more nucleotides in length." *Id.* at 6. Ultimately, the Office asserts that "applicant has not provided an adequate description of the genus of oligonucleotides that are useful, alone or in complexed formation so that one of skill in the art would be able to identify those that are useful from those that are not useful." *Id.*

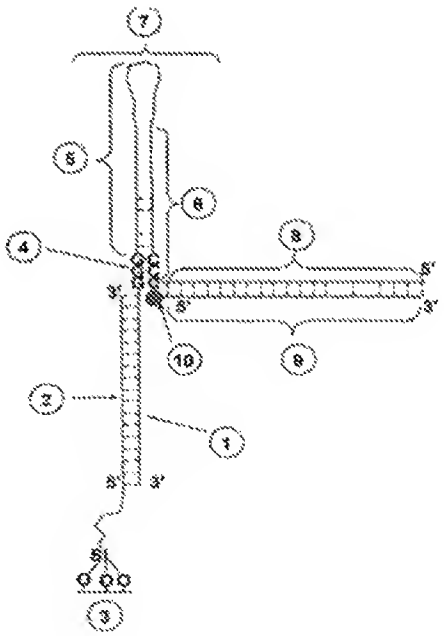
In addition, the Office construes the reporter element of the claims "as encompassing not only single-stranded nucleic acids, but also double-stranded nucleic acids, be it dsDNA, dsRNA, or DNA-RNA duplexes, and that the 'hybridization' that is taking place between the oligonucleotide and the reporter sequence can result in the formation of either duplex or triplex strands." *Id.* In short, the Office asserts that there is no description of how the various genera of reporter sequences are to be used in any method that has utility under 35 USC 101." *Id.* at 6. In particular, the Office concludes that sequences disclosed by the specification "present no embodiment of useful RNA molecules, no embodiment of triplex formation, and no embodiment of a useful DNA complex, much less an adequate description of those molecules that are useful such that one of skill in the art would be able to recognize/distinguish useful from non-useful molecules." *Id.* at 6-7. Applicants traverse this rejection for the following reasons.

First, one of skill in the art would have readily recognized a useful nucleic acid complex according to the claims because the specification discloses every structural feature of the claimed oligonucleotide complex. To emphasize these features, new claim 41 recites:

> A nucleic acid complex for detecting a target nucleic acid sequence comprising two discrete sequences:
>
> 1) a fluorophore-labeled reporter comprising a fluorophore attached to an oligonucleotide sequence;
>
> 2) an oligonucleotide having a stem-loop structure having a first stem section, a second stem section, and a tail sequence from the second stem section, wherein;
>
> a) the first stem section comprises at least one guanosine base,
>
> b) the tail sequence, is complementary to the fluorophore-labeled reporter oligonucleotide sequence,
>
> c) the loop comprises a sequence complementary to the target nucleic acid sequence; and
>
> wherein the fluorophore-labeled reporter is hybridized to the tail sequence of the oligonucleotide having a stem-loop structure, and the at least one guanosine base in the first stem section quenches the fluorophore.

Claim terms such as "stem loop," "hybridize," and "complementary," are universally known in the art and carry universally understood structural meanings. Moreover, Figures 1-4, and 6 offer detailed blueprints for constructing the claimed nucleic acid complex. Also, Figures 5, and 7-11 in conjunction with the disclosed Examples show the structure-function relationships between the components of the complex, and include exemplified complexes.

The table below also points out exemplary passages in the as-filed specification that provide written description support for each element of the claim 41. Figure 1 of the specification, which is included in the table, shows a graphical representation of the components of the claimed nucleic acid complex. Each component of the nucleic acid complex shown by Figure 1 is numbered, and the numbers are used as references in the passages contained in the table. As can be seen, each aspect of the claims is described in the specification. Accordingly, the claims have clear written description in Applicants' specification satisfying the written description requirement of § 112, first paragraph.

Claim Element	Location in Specification	Figure 1 from the as-filed Specification
A nucleic acid complex for detecting a target nucleic acid sequence comprising two discrete sequences	[0022] the present invention features methods for detecting the presence or absence of a target sequence [0038] The terms "target nucleic acid" refers to the nucleic acid sequence that is to be detected or measured using the improved methods of the present invention.	
comprising two discrete sequences	[0054] In one aspect, the present invention features a nucleic acid complex which comprises a capture oligonucleotide hybridized to a fluorophore-labeled probe sequence.	
a fluorophore-labeled reporter comprising a fluorophore attached to an oligonucleotide sequence	[0060] Finally, it can be seen in Fig. 1 that there is a "tail" structure consisting of unpaired nucleotides that form the 5' terminus of the capture oligonucleotide sequence. This 5' tail sequence 8 can be shorter or longer than that illustrated. The sequence of these bases is complementary to an oligonucleotide sequence called the reporter oligonucleotide 9. From the illustration, it can be seen that the reporter oligonucleotide has a fluorophore 10 attached at its 5' end.	
an oligonucleotide having a stem-loop structure having a first stem section, a second stem section, and a tail sequence from the second stem section	[0060] In this hairpin-forming sequence 6, the number of complementary bases can be shorter or longer than illustrated. Hybridization of these bases to their complementary bases results in the formation of a secondary structure called a hairpin or stem-loop 7. Finally, it can be seen in Fig. 1 that there is a "tail" structure consisting of unpaired nucleotides that form the 5' terminus of the capture oligonucleotide sequence.	
Wherein the first stem section comprises at least one guanosine base	[0060] Continuing in a 5' direction, the next required sequence is a series of guanosine (G) bases 4 in the positions indicated.	

Claim Element	Location in Specification	Figure 1 from the as-filed Specification
the tail sequence is complementary to the fluorophore-labeled reporter oligonucleotide sequence	[0060] it can be seen in Fig. 1 that there is a "tail" structure consisting of unpaired nucleotides that form the 5' terminus of the capture oligonucleotide sequence . . . The sequence of these bases is complementary to an oligonucleotide sequence called the reporter oligonucleotide 9.	
the loop comprises a sequence complementary to the target nucleic acid sequence	[0060] Next in the 5' direction is a sequence of nucleotides that are complementary to a sequence in the [target nucleotide sequence] to be measured	
and wherein the fluorophore-labeled reporter is hybridized to the tail sequence of the oligonucleotide having a stem-loop structure, and the at least one guanosine base in the first stem section quenches the fluorophore	[0061] The reduction in fluorescence emission when the fluorophore is in close proximity to the guanosine bases is known as G-base quenching and has been described in detail in the scientific literature	

According to the MPEP, "[a]n adequate written description of the invention may be shown by any sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP at § 2163(B)(II)(3)(a). (citations omitted). Evidence that Applicant was in possession of the claimed invention may include complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956,964, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Applicants submit that one of skill in the molecular biology arts could look to the specification and find all information that is necessary to construct and use a nucleic acid complex according to the claims. Here, the teachings contained in the specification alone, and even more in combination with

the knowledge that one of skill in the art possesses[1], satisfies the written description requirement as expressed by *Enzo* and the MPEP.

While the Examiner has not made a rejection under 35 U.S.C. § 101, but mentioned it at the Interview, and briefly alluded to it in the rejection under § 112 on page 6 of the Final Office Action, the claimed complexes are used to detect target sequences. Indeed, one of skill in the art that wants to use a nucleic acid complex according to the claims to detect a target sequence would include a nucleic acid sequence that is complementary to the target sequence in the loop structure of the complex. *See* Specification at ¶¶ [0023] and [0038].

The Office also relies on the Federal Circuit's guidance in *Alonso* (88 USPQ 2d 1849 (Fed.Cir. 2008), that "the specification must describe the invention in sufficient detail so 'that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought,'" to allege that the specification fails to provide appropriate written description support. Office Action at 10. However, *Alonso* dealt with the failure of one exemplified monoclonal antibody to support a broad claim directed to all anti-idiotype antibodies useful for treating neurofibrosarcoma. *Alonso's* outcome was reasonable given the fact that there is no general structure of antibody recognition sequences, or of idiotypes. Here, however, as discussed above, the specification discloses complete written and graphical depictions of the claimed physical structure of the claimed complex, as well as discusses and exemplifies the relationship between the structural changes that result from having the stem region bound to a complementary sequence, rather than forming a stem-loop, as well as the implication of

1 See, for example, US Patent Application Publication 2003/0003486 A1 (Sauer et al.), cited by the Office in the current Office Action.

that binding on the fluorescence signaling capacity of the complex. In addition, the skilled artisan using the claimed invention would have designed the sequence in the loop structure of the claimed nucleic acid complex that is complementary to the target sequence. Therefore, as opposed to the unknowable anti-idiotype amino acid sequences in *Alonso*, the target sequence aspect of the invention is always known by the artisan, and thus is always useful, and need not be explicitly taught by the specification.

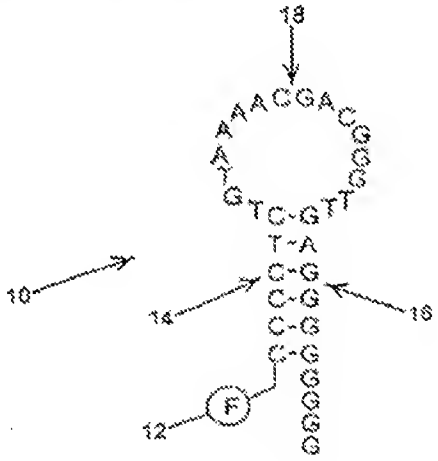
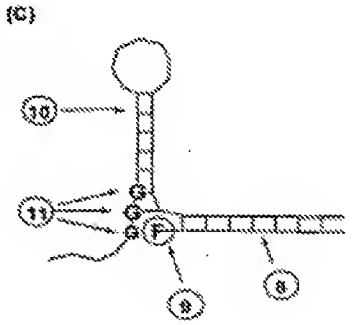
In sum, for the reasons discussed above, Applicants submit that the claims find written description support in the specification that meets the requirements set forth by the MPEP and *Enzo*. The specification also describes the genus of claimed nucleic acid complexes in satisfaction of the standard communicated by *Alonso*. Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

V. Rejection under 35 U.S.C. §§ 102(e) and 103(a)

Claims 16, 20, 23, and 24 stand rejected under 35 U.S.C. § 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a), as being obvious under US Patent Application Publication 2003/0003486 A1 (Sauer et al.). Office Action at 12. Applicants traverse this rejection. As new claims 41-43 replace claims 16, 20, and 23, and claim 24 is canceled, the following remarks effectively apply to the new claims.

In order for a reference to be anticipatory, it must teach all the elements of the claims. *See* MPEP 2131 ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.") (citation omitted). Here, Applicants respectfully submit that Sauer fails to teach all of the elements of the claims. More specifically, independent claim 41 dictates

that the recited nucleic acid complex *must* comprise two oligonucleotides, a fluorophore-labeled reporter oligonucleotide sequence and an oligonucleotide having a stem-loop structure. In other words, the oligonucleotides are discrete, and not linearly associated. By contrast, the only oligonucleotide structure Sauer discloses comprises a *single* oligonucleotide, wherein the fluorophore/dye molecule is attached to the same oligonucleotide that contains a stem-loop structure. *See,* for example, Sauer at Abstract and Fig. 3. This difference between the Sauer oligonucleotide and the claimed nucleic acid complex is shown in the comparison below of the Sauer oligonucleotide to the claimed nucleic acid complex.

Figure 3 of Sauer	**Figure 2C of the as-filed Specification**
	

According to Sauer, Figure 3 shows "a . . . dye-labeled oligonucleotide in which the stem sections are hybridized to one another." *See* Sauer at ¶ [0036]. Thus, neither the drawing of the Sauer oligonucleotide, nor Sauer's description of the drawing disclose more than a single oligonucleotide sequence. By contrast, Figure 2C of the Specification shows two, discrete oligonucleotides, "a **reporter oligonucleotide** (No. 8)

with an attached fluorophore (No. 9) hybridized to a **single-stranded oligonucleotide** with the potential of forming a hairpin or stem-loop configuration (No. 10) will have its fluorescence emission quenched if there are guanosine bases (No. 11) in the vicinity of the fluorophore (No. 9) when the structure is in the hairpin or stem-loop configuration (No. 10)." *See* Specification at ¶ [0061]. Again, whereas the single Sauer oligonucleotide is attached to a fluorophore/dye, and contains a stem-loop, the stem-loop sequence and the fluorophore of the claimed complex are contained on *separate* oligonucleotides. Thus, as stated by Applicants above, Sauer does not teach the element of the claims pertaining to attaching a fluorophore to *an oligonucleotide that is separate* from an oligonucleotide that can form a stem-loop structure. Therefore, Sauer does not anticipate the claims. Moreover, as Examiner-cited art must also teach all the limitations of the claims to make a *prima facie* case of obviousness, Sauer also does not render the claims obvious. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 16, 20, 23, and 24 under 35 U.S.C. §§ 102(e) and 103(a).

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

If the Examiner believes a telephone conference could be useful in resolving any outstanding issues, the Examiner is respectfully invited to contact Applicants' undersigned counsel at (703) 776-9703.

Respectfully submitted,

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